Remarks

The present invention provides methods for treating subjects having a variety of disease states which are the result of neoplastic cell proliferation of cells which express peroxisome proliferator activated receptor-gamma (PPAR-γ), especially myelogenous leukemia cells whose growth is mediated by PPAR-γ. Invention methods comprise the use of a composition comprising a combination of at least one PPAR-γ-selective activator having defined structure and at least one retinoid X receptor (RXR) selective agonist. As amended herein, the claims focus specifically on the use of a combination of (1) PPAR-γ-selective prostaglandins having a defined structure (as the PPAR-γ-selective activator) and (2) a RXR selective agonist. Treatment of leukemia cells with the invention combination results in an enhanced effect relative to the effect provided by either agent individually.

By the present communication, claims 1, 3, 19 and 20 have been amended to define Applicants' invention with greater particularity. No new matter has been introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. See, for example, page 14, ll. 30-45 of the specification where "structure II" is described in detail. In view of the amendments submitted herewith, claims 2, 5-11 and 14-18 have been cancelled without prejudice, subject to Applicants' right to pursue cancelled subject matter in continuation or divisional applications claiming priority to the instant application. Thus, the present communication reduces the number of claims under consideration and places the remaining claims in condition for allowance, or at a minimum, in better condition for appeal. Accordingly, entry of the amendments submitted herewith is respectfully requested.

Upon entry of the amendments submitted herewith, claims 1, 3, 4, 12, 13, 19 and 20 will remain pending in the application. The present status of all claims in the application, and current amendments thereto, are provided in the Listing of Claims presented herewith beginning on page 2 of this communication.

Interview Summary

Courtesies extended to Applicants' representative during the telephone interview conducted on March 21, 2006, during which the rejections asserted in the February 6, 2006 Office Action were discussed, are acknowledged with appreciation. The following remarks contain the substance of the discussion.

The Rejection of claims 1-20 under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1-20 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. Applicants respectfully disagree with the Examiner's conclusion that the specification allegedly does not provide enablement for all substances encompassed by the terms "PPAR-γ-selective prostaglandin" and "retinoid X receptor agonist."

Contrary to the Examiner's conclusion, Applicants respectfully submit that the specification provides ample enablement for all substances encompassed by the terms "PPAR-γ-selective prostaglandin" and "retinoid X receptor agonist." The Examiner's conclusion is unsupported and based on an erroneous evaluation of the Wands factors, and thus fails to meet the Examiner's burden of proof.

The M.P.E.P. states that the "examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. §2164.04 (emphasis added). Applicants respectfully submit that the Examiner has clearly failed to meet this burden of proof. The Examiner has failed to provide any reasoning or evidence to support the assertion that the combinations of PPAR-γ-selective prostaglandins and RXR agonists encompassed by the claims cannot be used as required by the present claims, i.e., for the treatment of myelogenous leukemia.

There is no reason to suspect, a priori, that an RXR agonist, such as one of the many examples listed on p. 19, l. 29 to p. 21, l. 26 of the specification, will not have the same or

similar functional activity when combined with a PPAR-γ-selective prostaglandin having structure II as demonstrated for the exemplary combination, LG268 and PG-J2.

In addition to the failure to provide any reason to doubt that these above-mentioned RXR agonists could be combined with PPAR-γ-selective prostaglandins having structure II, the Examiner has failed to take into consideration the numerous references that demonstrate that RXR agonists were well known in the art and widely available at the time of filing.[1] Anyone of ordinary skill in the art would be able to recognize RXR agonists. In addition, one or ordinary skill in the art would also be able to employ methods of identifying RXR agonists given what was available in the art at the time of filing. The Examiner has provided no reason to question the operability of the combination of an RXR agonist and a PPAR-γ-selective prostaglandin for inhibiting growth in diseases such as myelogenous leukemia. The Examiner has, therefore, failed to meet the burden of proof needed to support an enablement rejection.

Further evidence of the Examiner's failure to establish a lack of enablement for the present claims is based on an erroneous evaluation of the Wands factors, 8 USPQ2d 1400 (CAFC 1988) at 1404, as follows.

1 and 2) The nature of the invention and relative skill of those in the art (pp. 4-5 of the Office Action)

With respect to these two parameters, the Examiner has correctly characterized the invention (which is drawn specifically to methods of inhibiting or reducing growth of myelogenous leukemia cells where growth is mediated by PPAR-γ) and properly acknowledged that the level of relative skill in the relevant art is high.

[1] *See e.g.*, Nagy, et al., 15(7) Molecular and Cellular Biology 3540-51 (1995) and U.S. Patent Nos.: 5,271,103; 5,399,586; 5,455,265; 5,618,836; 5,672,710; 5,780,676; 5,906,920; 5,962,731; 5,696,104; 6,043,279; 6,130,230; 6,147,255; 6,162,815; 6,172,115; 6,653,322; 6,627,652; 6,320,074; 6,388,105; and 6,403,638.

3) The breadth of the claims (p. 5 of the Office Action)

Applicants respectfully disagree with the Examiner's assertion that the instant claims are "deemed very broad" (see p. 5, l. 1 of the Office Action). As amended herein and suggested by the Examiner during the telephone interview, the claims are directed to methods employing defined compositions, wherein PPAR-γ-selective activators of the claimed composition are defined both functionally (e.g., PPAR-γ-selective prostaglandins) and structurally (e.g., structure II). As long as a compound meets the structural and functional requirements set forth, it is clearly within the scope of the present claims.

For retinoid X receptor agonists contemplated for use herein, all compounds with the ability to activate an RXR receptor would be expected to react similarly to the exemplary RXR agonist LG268.[2] Given what was known in the art at the time of filing, one of ordinary skill in the art would fully expect any compound which is recognized in the art to be an RXR agonist would be suitable for use in the practice of the presently claimed invention.

4) The amount of direction and guidance presented (pp. 5-6 of the Office Action)

Applicants respectfully disagree with the Examiner's assertion that "Applicant's functional language at the exact point of novelty fails to meet the requirements set forth under 35 U.S.C. § 112, first paragraph" (see p. 6, ll. 10-11 of the Office Action). As amended, the claims define PPAR-γ-selective prostaglandins contemplated for use herein by both structure (e.g., structure II) and function (e.g., prostaglandins selective for PPAR-γ). See also the extensive discussion of prostaglandins having structure II at p. 14, ll. 19-45 of the specification.

With respect to RXR agonists, all compounds recognized in the art to be RXR agonists would be expected to react similarly to the exemplary RXR agonist LG268, as demonstrated in

[2] *See supra*, note 1 (listing numerous exemplary references available at the time of filing regarding the large number of RXR agonists known in the art at the time of the present invention).

the specification.[3] Given what was known in the art at the time of filing, one of ordinary skill in the art would fully expect any such RXR agonists to be suitable use in the practice of the invention as presently claimed. Applicants respectfully submit that ample guidance has been provided to carry out the method contemplated by the present claims.

5) The predictability of the art (pp. 6-8 of the Office Action)

Applicants respectfully disagree with the Examiner's assertion that the present invention is highly unpredictable because one allegedly cannot "recognize the identity of the members of the genus, by structure, formula, or chemical name" (see p. 7, ll. 3-5 of the Office Action; emphasis in original). With respect to PPAR-γ activators, the claims as amended herein define PPAR-γ activators contemplated for use in the practice of the present invention with reference to both structures and chemical names of the members of the contemplated genus, in addition to the functional requirement that the compounds are PPAR-γ activators. With respect to RXR activators, the specification identifies numerous compounds which were known in the art to be RXR activators at the time the present application was filed; moreover, mere reference to "RXR activator" at the time of filing would have been readily recognized by one of skill in the art to embrace the numerous classes of compounds described in the extensive art which existed at the time of filing (see footnote 1 supra). Accordingly, it is respectfully submitted that the invention, as defined by the claims as amended herein, is highly predictable.

6 and 7) The presence or absence of working examples and the quantity of experimentation necessary (pp. 9-10 of the Office Action)

Applicant respectfully disagrees with the Examiner's assertion that the use of "a single combination of PG-J2 and LG268" (see p. 9, ll. 2-3 of the Office Action) is not commensurate in scope with the claims. The combination provided is exemplary of ligands contemplated for use herein and demonstrates the general utility of combinations of these families of ligands (i.e.,

[3] *See supra*, note 1 (listing numerous exemplary references available at the time of filing regarding the large number of RXR agonists known in the art at the time of the present invention).

PPAR-γ selective activators and retinoid X receptor agonists). Given structure II of PPAR-γ selective prostaglandins, as well as the extensive list of exemplary RXR selective ligands on p. 19, l. 29 to p. 21, l. 19 of the specification) each of which would be expected to operate in substantially the same way, additional examples with further members would merely be superfluous. Therefore, the claims should not be limited to just the working examples provided. Quantity of experimentation is only one factor involved in determining whether undue experimentation is required; moreover, time, and difficulty of experiments are not determinative if they are merely routine (MPEP § 2164.06).

Further evidence of the improper evaluation of the present specification and claims under Wands is reflected by the fact that the Examiner has totally failed to take into account the following Wands factor:

8) State of the prior art

The Examiner has not provided any references indicating the state of the art with respect to PPAR-γ-selective activators or retinoid X receptor agonists for treatment of myelogenous leukemia cells expressing PPAR-γ. The state of the art is advanced regarding retinoid X receptor agonists in general and activators such as prostaglandins are a well known class of compounds. However, only the present claims contemplate use of combinations of PPAR-γ-selective activators and retinoid X receptor agonists for treatment of myelogenous leukemia cells expressing PPAR-γ.

Furthermore, the claimed methods do not contemplate using just any PPAR-γ-selective activator, but instead require the use of PPAR-γ-selective prostaglandins, i.e., prostaglandins of structure II. Such defined prostaglandins are required to be used in combination with RXR agonists, which were well known in the art at the time of filing, as evidenced by the availability of numerous publications and patents at the time of filing. Given the clear definition of PPAR-γ-selective prostaglandins contemplated for use herein, and the extensive art which existed at the

time of filing with respect to RXR agonists (see footnote 1 supra), it is respectfully submitted that the state of the art is high in regard to the claimed subject matter.

In summary, it is respectfully submitted that the specification provides more than adequate enablement of the claimed methods. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-20 under 35 U.S.C. § 112, first paragraph.

The § 103(a) Rejection over Kato et al. in view of Boehm et al. or Nadzan et al.

The rejection of claims 1-4, 11-14, 16, and 19-20 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kato et al. (Cancer Research 46:3538-3542, 1986) in view of Boehm et al. (J.Med. Chem. 38:3146-3155, 1995) or Nadzan et al. (Book of Abstracts, 211th ACS National Meeting, New Orleans, LA, March 24-28, 1996) is respectfully traversed.

The present invention, as defined, for example, by claim 1, distinguishes over Kato et al. by requiring administration of a combination of a defined PPAR-γ–selective activator and RXR selective activator to myelogenous leukemia cells whose growth is mediated by PPAR-γ. The present invention inhibits or reduces neoplastic leukemia growth by employing a combination of PPAR-γ-selective prostaglandins (having structure II) with RXR agonists (which were well known in the art at the time of filing).

Kato et al. does not disclose or suggest the present method. Indeed, as acknowledged by the Examiner, "Kato et al. does not expressly disclose the employment of the combination" (see p. 11, l. 6 of the Office Action). Instead Kato et al. merely focuses on the correlation of antitumor and diarrhea-inducing activities of various prostaglandins and derivatives. Kato et al. does not teach or suggest using anything else in combination with a prostaglandin.

Boehm et al. is unable to cure the deficiencies of the primary reference. Indeed as acknowledged by the Examiner, Boehm et al. contemplates the use of RXR selective retinoids or

agonists for "inducing apoptosis in leukemia cells" (see p. 11, l. 14 of the Office Action). In contrast, the present invention requires the combination of a defined PPAR-γ-selective activator and an RXR selective activator to inhibit or reduce growth of myelogenous leukemia cells whose growth is mediated by PPAR-γ. Boehm et al. does not teach or suggest a combination as required by the claimed methods.

Further reliance on the Nadzan et al. abstract is also unable to cure the deficiencies of the primary reference. Similar to Boehm et al. as discussed above, Nadzan et al. merely mentions the use of RXR activators, but does not teach or suggest a combination with another compound as required by the claimed methods.

Applicants respectfully submit that the combination of references does not meet each and every requirement of the claims. Moreover, one of ordinary skill would have no motivation to combine the applied references. There is no teaching or suggestion in the references to combine the individual components of each reference with any other compound. Thus, there is no indication that PPAR-γ-selective activators and RXR selective activators work in conjunction with each other to inhibit growth of leukemia cells. Nor is there any indication in the art to suggest a cooperative interaction, much less a cooperative result.

Even if there were motivation to combine, there would be no reasonable expectation of success. In an effort to support such an expectation, the Examiner asserts that "all active composition components herein are known" and "considered prima facie obvious to combine them into a single composition useful for the very same purpose" (see p. 13, ll. 1-3 of the Office Action). Contrary to the Examiner's assertion, none of the references suggests the role of PPAR-γ in leukemia cells or recognizes that modulation of PPAR-γ is a key element in the success of the claimed methods. Therefore, a person skilled in the art would have no reason to expect success in light of the references.

Applicants respectfully submit that a reference can only be used for what it fairly teaches. Hindsight provided by the application at issue cannot be used to provide the missing motivation or expectation of success. None of the references discloses the combination of PPAR-γ activator and RXR agonist required by the present claims; none of the cited references, taken alone or in combination, provide any motivation for skilled artisans to combine the compounds shown in the references. Furthermore, there is no teaching in the references that would suggest that any combination of activators would have a reasonable expectation to succeed in the claimed method. Accordingly, reconsideration and withdrawal of the rejection of claims 1-4, 11-14, 16 and 19-20 rejected under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to contact the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date 5/5/06

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